Clinical Investigation Plan

TITLE	Effect of use of DryNites® absorbent pants on the rate of spontaneous resolution of paediatric nocturnal enuresis (NE)
STUDY TREATMENT	DryNites® (Medical Device Class I)
PHASE OF DEVELOPMENT	IV
VERSION	3.0 Final: 28 January 2022 Amendment #: 2
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NCT04620356

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List of Abbreviations

AE	Adverse event
ADE	Adverse device effect
ANCOVA	Analysis of covariance
BMI	Body mass index
CE mark	Certification mark that indicates conformity of the product with the requirements of the applicable European Community directives
CI	Confidence interval
CIS	Checklist Individual Strength
CRF	Case report form
CRO	Contract research organization
eCRF	Electronic case report form
EDC	Electronic data capture
EMEA	Europe, Middle East and Africa
GCP	Good clinical practice
ICF	Informed consent form
IEC	Independent ethics committee
IRB	Institutional review board
ISOIWRS	International Organization for Standardization
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NE	Nocturnal enuresis
NICE	National Institute for Clinical Excellence
PCP	Primary care provider
PDSS	Paediatric Daytime Sleepiness Scale
PinQ	Paediatric Incontinence Questionnaire
PRO	Patient-reported outcome
PT	Preferred term
QoL	Quality of life
SAE	Serious adverse event

SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
USADE	Unanticipated serious adverse device effect
WHOQoL	World Health Organization Quality of Life

Study Synopsis

<table>
<tr><td colspan="4">Full Study Title: Effect of use of DryNites® absorbent pants on the rate of spontaneous resolution of paediatric nocturnal enuresis (NE)</td></tr>
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<tr><td colspan="2">Number of Patients: 120</td><td colspan="2">Duration of Patient Participation:
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<tr><td colspan="2">Number of Sites: 7-12</td><td colspan="2">Duration of Study: 3 years</td></tr>
<tr><td colspan="4">Background and Rationale:
Nocturnal enuresis (NE) is stressful for both children and their parents/carers. Children vary in the age at which they achieve night-time dryness; in almost all cases, children will stop bed-wetting without any need for treatment. Use of absorbent pants for the management of NE is a controversial area, with many groups expressing conflicting opinions on the issue. Some experts believe that the use of absorbent pants can prevent the child from learning night-time bladder control, while others believe it has no impact on the rate at which children become dry. This study aims to show that using DryNites® absorbent pants in children with monosymptomatic NE does not have a negative effect on the speed that children become dry, compared with removing absorbent pants. It also aims to show that using DryNites® improves the overall quality of life (QoL) and sleep quality of both children and their parents/carers.</td></tr>
<tr><td colspan="4">Objectives:
Primary objective: to determine if discontinuing the use of DryNites® absorbent pants over a period of 4 weeks has any impact on the rate of spontaneous resolution of NE compared with continuing use of DryNites® absorbent pants.
Secondary objectives:
• To determine if using DryNites® absorbent pants improves the child's QoL assessed by the Paediatric Incontinence Questionnaire (PinQ) compared with not using absorbent pants
• To determine if using DryNites® absorbent pants improves the parent/carer's QoL assessed by the World Health Organization Quality of Life BREF (WHOQoL-BREF) compared with not using absorbent pants
• To determine if using DryNites® absorbent pants improves the child's sleep assessed by the Paediatric Daytime Sleepiness Scale (PDSS) compared with not using absorbent pants
• To determine if using DryNites® absorbent pants improves the parent/carer's sleep assessed by the Checklist Individual Strength questionnaire (CIS) compared with not using absorbent pants</td></tr>
</table>

Full Study Title: Effect of use of DryNites® absorbent pants on the rate of spontaneous resolution of paediatric nocturnal enuresis (NE)			
Phase:	Phase IV	**Type**:	Clinical Investigation
Number of Patients: 120		**Duration of Patient Participation**: 8 weeks (primary endpoint) – optional extension of 4 weeks	
Number of Sites: 7-12		**Duration of Study**: 3 years	

- To determine if DryNites® absorbent pants offer different benefits or limitations to previously used absorbent pants/nappies.

Study design:

This is an 8-week randomised, open-label, 2-arm, parallel-group Phase IV trial with a 2:1 allocation ratio for discontinuation or continuation of use of DryNites® absorbent pants in children with NE, and an optional 4-week extension period. This will be an equivalence trial for the primary endpoint.

Eligible patients are children with a clinical diagnosis of monosymptomatic NE, not previously treated for NE, and managed with absorbent pants/nappies (any brand) for a minimum of 6 months. Participants must be dry at day for at least 6 months. Participants will be divided in 2 age groups of similar size (4-<6 years and ≥6–8 years old).

The study consists of 3 consecutive periods of 4 weeks each, including the run-in, the intervention (core trial) period, and the extension period. During the 4-week run-in period, all participants will be assigned to using DryNites® every night. Participants meeting the inclusion criterion of NE 7 nights per week during the last week of the run-in period will be randomised in the intervention (core trial) period. During the 4-week intervention period, participants will be assigned to either stopping the use of absorbent pants or continuing DryNites® in a 2:1 ratio. All participants will receive absorbent bed mats to use every night, however, the use of bed mats is optional. During the 4-week optional extension period, participants will remain on their randomly assigned treatment for an additional 4 weeks.

Study specific mandated clinic or remote visits will be required as part of the participation in this study. Participants will be reimbursed for their travel expenses for on-site visits. Participants will be assessed on Day 0 (baseline), Day 28 ± 7days (end of run-in and randomisation), Day 56 ± 7days (end of intervention/core trial period), and Day 84 ± 7days (end of extension period). As a contingency to the restrictions due to the Covid-19 outbreak, the baseline, randomisation, and any subsequent visit (i.e., Visits 3 and 4) can also be performed remotely in case the patient cannot visit the site in person.

Dry and wet nights will be captured every day from the start of the run-in period to discontinuation of the study through an electronic diary, accessible through the parent's/carer's own device (smart phone, tablet, or computer).

QoL and sleep questionnaires will be completed in electronic format either on-site during the clinic visits or after the visit from randomisation onwards, using the parent's/carer's own electronic device. The perception of DryNites® attributes, compared to previously used absorbent products will be evaluated

through 2 specific questionnaires designed for this study, at study entry (for previous absorbent pants/nappies) and at the end of the run-in period (for DryNites®).

Study population:

The study will aim to randomise approximately 120 participants aged 4-8 years from a total of 7-12 sites in 3 countries (Belgium, Denmark, and the United Kingdom) over a 30-month enrolment period. Children/parents/carers actively seeking help for NE can be recruited via specialist centres, clinician visits, referrals, and collaboration with primary care providers.

Inclusion criteria

The following criteria must be met for the participant to be enrolled in the study:

1. Aged between 4-8 years at the time of enrolment
    a. To be categorised in the younger participant group, participants must be aged 4-<6 years
    b. To be categorised in the older participant group, participants must be aged ≥6-8 years
2. Have a clinical diagnosis of monosymptomatic primary NE
3. Have been dry in the day for ≥6 months prior to enrolment
4. Have on average no more than 1 dry night per month during the past 6 months at enrolment
5. Using absorbent pants/nappies to manage NE for at least 6 months prior to enrolment
6. Have an informed consent form (ICF) signed by their parent(s)/carer(s)
7. For randomisation: have NE 7 nights per week over Week 4/last week of the run-in period

Exclusion criteria

Patients meeting ANY of the following criteria are not eligible for participation:

1. Children in foster/court care
2. Have implemented any previous intervention to address NE (use of prescribed alarm schedule, desmopressin, imipramine, anticholinergics), or withdrawal of pants/nappies for >7 days in the previous 6 months
3. Have secondary NE
4. Have wetting in the day
5. Have faecal soiling
6. Have known urinary tract disease
7. Have diabetes

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8. Receive any regular intake of medication
9. Have a known developmental/neurological disorder
10. Have links to Kimberly-Clark of any kind (including family relations employed by Kimberly-Clark, holding stocks or shares in Kimberly-Clark)

Data collection/Data Sources:

Participants will be assessed on Day 0 (baseline), for demographics, height and weight, medical history, concomitant medication, prior use of absorbent pants/nappies, and full physical examination (optional). In case of remote visit, height and weight and full physical examination will be done when the visit is performed on-site. At Day 28 ± 7days (end of run-in and randomisation), Day 56 ± 7days (end of intervention/core trial period) and Day 84 ± 7 days (end of extension period), participants will be assessed for adverse events (AEs) since the previous visit, concomitant medication used to treat AEs, and patient-reported outcome (PRO) questionnaires. Baseline, randomisation, and any subsequent visit could be performed remotely via phone or video/teleconference, if an on-site visit cannot be performed. For remote visits, PRO questionnaires will be accessed through the parent's/carer's own electronic device and study materials (i.e., DryNites®, bed mats) will be shipped to the patient. The PRO questionnaires will be available after a given visit (and should be completed before the next visit). The PRO questionnaires can also be completed remotely, within the same time window, if completion is not feasible during any on-site visit including baseline. Dry and wet nights will be captured every day from the start of the run-in period to discontinuation of the study through an electronic diary, accessible through the parent's/carer's own device (smart phone, tablet, or computer).

Safety:

Adverse events, serious adverse events (SAEs), and medical device incidents will be monitored and reported throughout the entire course of the study. The AE reporting period begins when the patient is consented to participation in the study (date of informed consent signature) and continues through the study discontinuation date. Adverse events ongoing at study discontinuation will be followed up until resolution or stabilisation.

Data Management:

Investigators and site personnel will enter the data required by the clinical investigation plan using a fully validated and 21 CFR Part 11-compliant electronic data capture (EDC) system. All participating sites will have access to the entered data regarding the individual site of its own enrolled patients. For electronic patient-reported outcomes (ePROs), the data entered by the parents/carers will be directly captured into the EDC.

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<tr><td colspan="4">Statistical Considerations:
The analysis sets will be the following: Screened Set (all patients enrolled), Randomised Set, Primary Analysis Set (all patients randomised without major violation of the clinical investigation plan), Extension Set.
Demographic and baseline characteristics, disease history, physical examination and medical history will be summarised with appropriate descriptive statistics by group and separately for age subgroups on Screened and Randomised Sets.
The Absorbent Pants Clinical Trial Questionnaire administered at study entry, and the DryNites® Clinical Trial Questionnaire administered at the end of the run-in period, will be analysed descriptively for the Screened Set.
Direct-to-patient data will be analysed descriptively at each assessment along with applicable change from baseline on Randomised and Primary Analysis Sets.
The primary outcome (i.e., average number of wet nights in Week 4 of the core study period) will be analysed on the Primary Analysis Set comparing the 95% confidence interval (CI) for the difference between the means of the 2 groups with the predefined margin ($\delta = 2/7$). If the CI lies strictly within [$-\delta$, $+\delta$], the study hypothesis will be demonstrated. The primary outcome will be then presented by age group (4–<6 years, ≥6–8 years).
Secondary outcome will be presented by group on Randomised Set. Frequency distribution and descriptive statistics, when applicable, will be provided by visit for each item of questionnaires, while summary statistics for total scores, domain scores and changes from baseline will be provided as applicable for the PinQ, the WHOQoL-BREF, PDSS and CIS. The effect size will also be presented as descriptive statistics of ratio between the change from baseline and baseline standard deviation (SD). The percentage of patients with change from baseline ≥0.5 time the SD will also be provided.
For applicable questionnaires, a covariance analysis model (ANCOVA) with baseline PROs value as covariate will be performed. Group comparisons will be performed for the difference in least squares means (LSMean) at Day 56 ±7 days. The same analysis will be repeated using a repeated measure model to assess the extension period effects.</td></tr>
</table>

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<tr><td colspan="4">For each group, numbers and proportion of treatment-emergent adverse events (TEAEs), device-related TEAEs, serious TEAEs and medical device incidents will be tabulated by preferred term and system organ class. All safety analyses will be performed on the Safety Analysis Set. All the events occurred from ICF signature till randomisation will be described separately.
Sample size
The statistical hypothesis behind the present study design is the equivalence in rate of spontaneous resolution of NE at 56 ±7 days between discontinuing and continuing nocturnal use of DryNites® absorbent pyjama pants in children with NE. The margin for non-inferiority is set to 2/7 wet nights with an expected proportion of 0.95 and 0.80 wet nights, respectively for continuing and discontinuing use of absorbent pants group. The power is set to 99%.
Fifteen participants are needed in the continuation arm to obtain a power of 99%. This means that a total of 45 participants are needed at randomisation (due to the 2:1 randomisation). Fifteen additional participants are added to this number (total of 60 participants) to compensate for dropouts/poor compliance during the trial, and for the participants who will be excluded at randomisation because they did not fulfil the criteria of 7 wet nights per week. Additionally, the primary endpoint will be analysed separately for the 2 age groups (4–<6 and ≥6–8 years of age) and therefore 60 participants will be needed for each age group (total 120 participants).
As such, 120 participants should be recruited, with approximately half of the participants should be in the younger age group, age 4–<6 years, and half of the participants should be in the older age group, ≥6–8 years.

Interim and Final Analyses:
No interim analyses are planned. The primary and secondary analysis will be performed after the completion of 4 weeks post randomisation phase. Applicable analyses will be repeated at the end of the extension period.</td></tr>
</table>

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<tr><td colspan="4">Ethical and Regulatory Considerations:
This clinical investigation will be conducted in accordance with the clinical investigation plan and all applicable laws and regulations including, but not limited to Good Clinical Practices (GCP), International Organization for Standardization (ISO) 14155, the Directive 93/42/EEC and Regulation 2017/45/EU, as applicable, and the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the General Data Protection Regulation (EU) 2016/67. An Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) must review and approve the clinical investigation plan, ICF and paediatric assent form (where applicable by local regulations) before any patients are enrolled. The parents/legally authorised representatives of the patient must sign and date the IRB/IEC-approved informed consent form before any clinical investigation plan-directed data collection is performed.</td></tr>
</table>

Documentation of Amendments to the Clinical Investigation Plan

Amendment #2: 28 January 2022

Sections modified and updates	Reason
4.1 Study design All participants will receive absorbent bed mats to use every night, however, the use of bed mats is optional.	Text has been updated to reflect the optional use of bed mats.
4.3 Study population The study will aim to randomise approximately 120 participants aged 4-8 years from a total of 7-12 sites in 3 countries (Belgium, Denmark, and the United Kingdom) over a 30-month enrolment period.	Extension of study recruitment from 15 to 30 months due to low recruitment during the Covid-19 pandemic period.
4.3.8 Clinical investigation plan deviations The following events will be considered as the major violations of the clinical investigation plan and lead to the exclusion of the participant's data from the analysis: • Absorbent pants/nappies (of any brand) used nocturnally in the 'no pants' group (up to 4 violations of the clinical investigational plan over the 4-week trial period will merit exclusion; these will be documented in the diary) • No pants, or absorbent pants of a different brand, used nocturnally in the DryNites® group (up to 4 violations of the clinical investigation plan over the 4-week trial period will merit exclusion; these will be documented in the diary) • Initiation of a prescribed therapy for NE (pharmacologic or bed alarm)	The number of individual violations required to define a major violation and exclude the data from the analysis has been relaxed to "up to 4" instead of "≥3 violations".
4.4.2 Provision of Study Treatment Study treatment and absorbent bed mats will be supplied to the participants by the Investigator/site; however, the use of bed mats is optional.	Text has been updated to reflect the optional use of bed mats.
4.5.3.2 Physical examination The baseline visit can be performed remotely. In case a remote baseline visit is performed, height/weight and full physical examination will not be recorded. In this scenario, the Investigator must check the medical records and/or interview the parent/carer to investigate history of congenital abnormalities of the urinary tract, history of surgery on the urinary tract, and history of verified urinary tract infections before determining eligibility.	Text has been updated to reflect that baseline visits can be performed remotely as well. In case of a remote visit, the Investigator must check the subject's history of verified urinary tract infections, congenital abnormalities of the urinary tract, and surgery on the urinary tract to determine eligibility.

Table 2 Schedule of assessments Table footnotes: (a): Baseline visit can be performed remotely. (b): In case a remote visit was performed, height/weight will not be recorded. (c): In case a remote visit was performed, a full physical examination will not be recorded. In this scenario, the Investigator must check the medical history and/or interview the parent/carer to investigate history of congenital abnormalities of the urinary tract, history of surgery on the urinary tract, and history of verified urinary tract infections. (d): AEs, SAEs and Medical Device Incidents are collected from ICF signature onwards. (e): Review of diary data by the Investigator/treating physician. (f): For participants who meet the randomisation criterion. (g): For all participants at the end of the run-in period.	Footnote text has been updated to reflect that the baseline visit can be performed remotely when an on--site visit is not possible and add clarity on height/weight record and physical examination in case of a remote visit.
4.7.1 Visit 1 - baseline visit Baseline visit can be performed remotely. *In case a remote visit was performed, height/weight will not be recorded. **In case a remote visit was performed, a full physical examination will not be performed. The Investigator must check history of congenital abnormalities of the urinary tract, history of surgery on the urinary tract, and history of verified urinary tract infections.	Text has been updated to reflect that the baseline visit can be performed remotely and add clarity on how height/weight and the physical examination will be recorded in case of a remote visit.

Additional minor changes have been made to maintain consistency of the document.

Milestones

Milestone	Timelines
Final clinical investigation plan	11 Sep 2019
First patient in	21 Feb 2020
Last patient out	Q4 2022
Final report of study results	Q2 2023

Abbreviations: Q: quarter.

1 INTRODUCTION

1.1. Background

Nocturnal enuresis (NE) is a stressful occurrence for both children and their families, which can have negative emotional and social implications for sufferers (NICE 2014, NICE 2010).

It can significantly reduce the child's self-esteem, increase the likelihood of behavioural problems, and impact their attachment style (Coppola et al. 2011). It can also lead to increase in parental anxiety and depression (Tanriverdi et al. 2014, Meydan et al. 2012).

In addition, NE can lead to poor quality, interrupted sleep for both sufferers and their families (NICE 2014, NICE 2010, Ertan et al. 2009). To add to this, the burden of bed-wetting is frustrating and costly to families (NICE 2014, Paediatric Society of New Zealand 2005). As children in Europe often begin school at age 4–5 years, many families become interested in resolving enuresis at this age.

Absorbent pants may reduce the impact of NE on the quality of life (QoL) of both children and their families, through reducing the burden and cost of wet beds, and reducing night-time awakenings (Urology Care Foundation, Kushnir et al. 2013).

Guideline recommendations on the management of NE are not comprehensive, and while many treatment options are available, advice on use of absorbent pants is limited (NICE 2014, NICE 2010, Paediatric Society of New Zealand 2005, Urology Care Foundation, Nevéus et al. 2010, Feldman 2005).

Use of absorbent pants for the management of NE is a controversial area, with many groups expressing conflicting opinions on the issue. Some recommend against using absorbent pants, stating that they reduce the incentive for children to become dry and can delay attainment of dryness (Uptodate, Nocturnal enuresis, Fleming 2012). Even though undocumented, in many countries (e.g., China, Sweden, and Germany) health care professionals (HCPs) recommend against using absorbent pants to manage NE.

1.2. Rationale

No evidence is available to suggest that the use of absorbent pants slows resolution of NE, or that removal of absorbent pants improves resolution of NE.

Furthermore, there are currently no evidence-based recommendations supporting the use of absorbent pants for management of NE, and the lack of clear guidance supporting the benefits

of using absorbent pants may have resulted in many children and their families not benefitting from this possible solution.

As such, this study aims to demonstrate that continuing nocturnal use of absorbent pants in children with NE does not have a negative impact on the rate of spontaneous resolution of NE, compared with discontinuing use of absorbent pants. It also aims to show that use of absorbent pants may provide additional QoL and sleep benefits for both children and their parents/carers. The age group 4–8 years is recommended for inclusion in this study, as this will involve families who become interested in resolving enuresis before or shortly after starting school. Age 8 years was chosen as the cut-off, as by this age many children who continue to experience NE will have been exposed to treatment of some sort.

Nocturnal Enuresis can vary in severity from 1 night per week to every night per week. This study will evaluate children with severe NE, who usually experience NE every night of the week. Although the rate of spontaneous resolution is low in this group, it is the most appropriate and reliable population to study. Children who experience NE for <7 nights per week are a heterogeneous group whose rate of NE may vary weekly; as such, many confounding variables could affect the trial results if this population was used.

1.3. **Lay Summary**

Bed-wetting is stressful for both children and their parents/carers. In almost all cases, children will stop bed-wetting without any need for treatment. Children vary in the age at which they achieve night-time dryness. Regardless of whether or not a parent/carer chooses to use a medical treatment to help speed up achievement of night-time dryness (e.g., use of an alarm or medication), night-time use of absorbent pants can help to reduce the burden of wet beds until the child is completely dry every night. Some experts believe that the use of absorbent pants can prevent the child from learning night-time bladder control, while others believe it has no impact on the rate at which children become dry. This study aims to show that using DryNites® absorbent pants does not have a negative effect on the speed that children become dry, compared with removing absorbent pants. It also aims to show that using DryNites® improves the overall quality of life and sleep quality of both children and their parents/carers.

2 BENEFIT/RISK AND ETHICAL ASSESSMENT

DryNites® pyjama pants are absorbent pants designed to reduce the burden of bed-wetting, commercially available since 1995. DryNites® are registered as class I medical devices and CE marked[1]. They are not a treatment for NE and are not designed to cure NE.

The side-effects of using DryNites® have not been evaluated in any studies. Minor side-effects may include sweating or rash (Cohen 2017). No severe side-effects are anticipated.

All trial participants will use DryNites® for the 4-week run-in period at the start of the trial. Following this, participants will be randomised to discontinue or continue use of DryNites® in a 2:1 ratio for another period of 4 weeks (the discontinuation of the use of pants being the intervention). There is no placebo comparator in this trial. Safety will be monitored at each trial visit. The parents of trial participants will be asked whether the child has experienced any side-effects or discomfort while wearing the DryNites®.

In addition, all participants will be provided with DryNites Bed Mats to be used during the study period, however, the use of bed mats is optional.

3 OBJECTIVES AND ENDPOINTS

The aim of this trial is to demonstrate if discontinuation of nocturnal use of absorbent pants in children with NE has any impact on the rate of spontaneous resolution of NE, compared with continued use of absorbent pants, over a period of 4 weeks. It is hypothesised that children discontinuing or continuing the use of absorbent pants will show statistically equivalent outcomes (number of dry nights) at the end of a 4-week trial period.

A secondary aim of this trial is to demonstrate that the continued use of absorbent pants has a positive impact on QoL outcomes and sleep quality for both parents and children, compared with discontinuation of absorbent pants.

Study objectives and endpoints are listed in Table 1.

[1] Certification mark that indicates conformity of the product with the requirements of the applicable European Community directives.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine if discontinuing the use of DryNites® absorbent pants over a period of 4 weeks has any impact on the rate of spontaneous resolution of NE compared with continuing use of DryNites® absorbent pants	• Average number of wet nights in Week 8 (last week of the intervention period)
Secondary	
• To determine if using DryNites® absorbent pants improves the child's Quality of Life (QoL) assessed by the Paediatric Incontinence Questionnaire (PinQ) compared with not using absorbent pants	• Change from baseline in total PinQ score at Day 56 ± 7days
• To determine if using DryNites® absorbent pants improves the parent/carer's QoL assessed by the World Health Organization Quality of Life BREF (WHOQoL-BREF) compared with not using absorbent pants	• Change from baseline in total score of each domain at Day 56 ± 7 days
• To determine if using DryNites® absorbent pants improves the child's sleep assessed by the Paediatric Daytime Sleepiness Scale (PDSS) compared with not using absorbent pants	• Change from baseline in total PDSS score at Day 56 ±7 days
• To determine if using DryNites® absorbent pants improves the parent/carer's sleep assessed by the Checklist Individual Strength questionnaire (CIS) compared with not using absorbent pants	• Change from baseline in subscale scores at Day 56 ±7 days
• To determine if DryNites® absorbent pants offer different benefits or limitations to previously used absorbent pants/nappies	• Descriptive statistics

4 METHODOLOGY

4.1. Study Design

This is an 8-week randomised, open-label, 2-arm, parallel-group Phase IV trial with a 2:1 allocation ratio for discontinuation of continuation of use of DryNites® absorbent pants in children with NE, with an optional 4-week extension period. This will be an equivalence trial for the primary endpoint.

Eligible patients are children with monosymptomatic NE, not previously treated for NE, and managed with absorbent pants/nappies (any brand) for a minimum of 6 months. Participants must be dry at day for at least 6 months. Participants will be divided in 2 age groups of similar

size. The younger age group will be comprised of participants aged 4–<6 years old and the older age group will be comprised of participants aged ≥6–8 years old. Capping of the faster recruiting subgroup will be implemented if needed.

Participation in the study will be proposed for all children meeting the above conditions; parents/carers should be given sufficient time to review the study information and provide informed consent to their child's and their participation. Children's assent will be requested for the older age group.

The study consists of 3 consecutive periods of 4 weeks each, including the run-in, the intervention (core trial) period, and the extension period.

Participant meeting the eligibility criteria will enter the run-in period. During the 4-week run-in period, all participants will be assigned to using DryNites® every night.

Participant meets the inclusion criterion of NE 7 nights per week during the last week of the run-in period will be randomised to participate in the intervention (core trial) period. During the 4-week intervention period, participants will be assigned to either stopping the use of absorbent pants or continuing DryNites® in a 2:1 ratio. All participants will receive absorbent bed mats to use every night, however, the use of bed mats is optional.

Following completion of the 4-week intervention period, participants will be invited to participate in the optional 4-week extension. During the optional 4-week extension period, participants will remain on their randomly assigned treatment for an additional 4 weeks.

Study specific mandated clinic visits will be required as part of the participation in this study. Baseline, randomisation, and any subsequent visit (i.e., Visit 3 and 4) can also be performed remotely in case the patient cannot visit the site in person. Participants will be assessed on Day 0 (baseline), Day 28 ± 7days (end of run-in and randomisation), Day 56 ± 7days (end of intervention/core trial period), and Day 84 ± 7days (end of extension period).

Participants will be reimbursed for their travel expenses, where applicable.

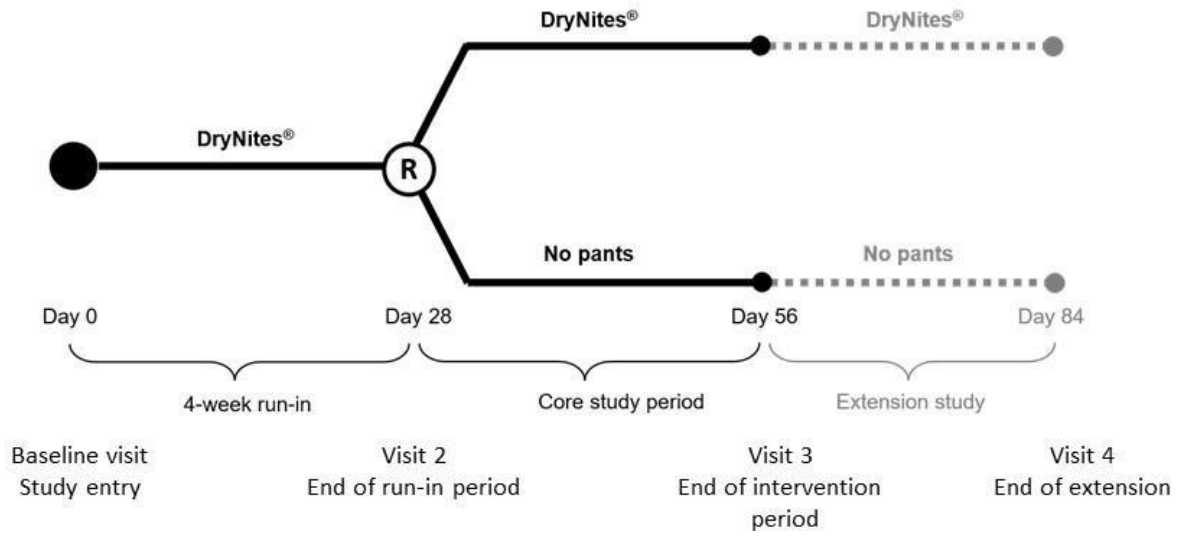
Dry and wet nights will be captured every day from the start of the run-in period to discontinuation of the study through an electronic diary, accessible through the parent's/carer's own device (smart phone, tablet, or computer).

Quality of life (QoL) and sleep questionnaires will be completed by children and parents/carers in electronic format on-site during the clinic visit, using site-based hand-held devices (e.g., tablets) or computers, from randomisation onwards. In case the questionnaires are not completed during the clinic visit or if a visit is performed remotely, the questionnaires will be accessible through the parent's/carer's own device. Questionnaires will be accessible after the visit and should be completed as close to the visit as possible (and before the next visit).

The perception of the absorbent products will be assessed by 2 questionnaires, at study entry (on previous absorbent products) and at the end of the run-in period (on DryNites®, compared to the previously used absorbent pants/nappies).

An overview of the trial design is provided in Figure 1.

Figure 1 Study Design



4.2. End of Study Definition

A patient is considered to have completed the study if he/she has completed all phases of the study including the last visit of the core trial period or the last scheduled procedure of the extension period.

The end of the study is defined as the date of last scheduled procedure for the last patient included in the optional extension period of the study globally.

4.3. Study Population

The study will aim to randomise approximately 120 participants aged 4-8 years from a total of 7-12 sites in 3 countries (Belgium, Denmark, and the United Kingdom) over a 30-month enrolment period. Children/parents/carers actively seeking help for NE can be recruited via specialist centres, clinician visits, referrals, and collaboration with primary care providers (PCPs).

Sites that are routinely involved in the care and treatment of patients with NE will be targeted for recruitment. Selection criteria and basic site information (e.g., site size, Investigator specialty, site type) will be collected via a site qualification survey.

All children/parents/carers actively seeking help and those who had not previously considered medical assistance, will be considered for study participation, and assessed for eligibility according to the defined selection criteria. A screening log will be maintained by each site to record the disposition of consecutive patients, potentially eligible for study participation.

The following options will be considered to reach the target enrolment:

- Advertising through notices in hospitals and PCP clinics may attract participants to the study
- Newspaper advertising could also be used.

4.3.1. Inclusion Criteria

The following criteria must be met for the participant to be enrolled in the study:

1. Patient aged between 4–8 years at the time of enrolment
    a. To be categorised in the younger participant group, participants must be aged 4-<6 years
    b. To be categorised in the older participant group, participants must be aged ≥6-8 years
2. Have a clinical diagnosis of monosymptomatic primary NE
3. Have been dry in the day for ≥6 months prior to enrolment
4. Have on average no more than 1 dry night per month during the past 6 months at enrolment
5. Using absorbent pants/nappies to manage NE for at least 6 months prior to enrolment
6. Have an informed consent form (ICF) signed by their parent(s)/carer(s)
7. For randomisation: have NE 7 nights per week over Week 4/last week of the run-in period

4.3.2. Exclusion Criteria

Patients meeting ANY of the following criteria are not eligible for participation:

1. Children in foster/court care

2. Have implemented any previous intervention to address NE (use of prescribed alarm schedule, desmopressin, imipramine, anticholinergics), or withdrawal of pants/nappies for >7 days in the previous 6 months
3. Have secondary NE
4. Have wetting in the day
5. Have faecal soiling
6. Have known urinary tract disease
7. Have diabetes
8. Receive any regular intake of medication
9. Have a known developmental/neurological disorder
10. Have links to Kimberly-Clark of any kind (including family relations employed by Kimberly-Clark, holding stocks or shares in Kimberly-Clark)

4.3.3. Patients Screening and Registration

The Investigator will:

1. Obtain signed informed consent from the parent(s)/carer(s) of the potential patient (and paediatric assent if applicable) before any study specific procedures are performed that are not part of routine medical care
2. Generate the patient's identification from the electronic data capture (EDC)
3. Determine patient's eligibility
4. Obtain a unique patient randomisation number through the Interactive Web Response System (IWRS). This number is part of the patient's identifier and will be maintained throughout the study

If a patient does not meet eligibility criteria or withdraws from participation in the study, then their number cannot be reused.

4.3.4. Screen Failures

Screen failures are defined as patients who were consented to participate in the study but are not subsequently randomly assigned to study treatment, for any reason identified before, during, or at the end of the run-in period.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information

includes demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

These patients should have the reason for study withdrawal recorded as 'Screen failure'; this reason for study withdrawal is only valid for patients who were not randomised.

Individuals who do not meet the criteria for randomisation in this study may be re-screened one time, after an additional run-in of 1 week.

4.3.5. Methods for Assigning Patients to Treatment Groups

A patient randomisation list will be produced using permuted block randomisation stratified by age group (4–<6 years old and ≥6–8 years old) and a 2:1 group allocation for discontinuation or continuation of the use of DryNites® pyjama pants.

When a patient is qualified for entry into the randomised treatment period, treatment assignment will be performed by means of an IWRS on a central level on Visit 2 (Day 28 ± 7 days).

Before the study is initiated, the log in information and directions for the IWRS will be provided to each study centre.

The Investigator or his/her delegate (study coordinator) will log on to the EDC and confirm that the patient fulfils the eligibility criteria and proceed with the randomisation. Participants will be assigned a unique number (randomisation number) in ascending numerical order on the next available record in the group at each study centre. The randomisation number encodes the participant's assignment to 1 of the 2 arms of the study (No Pants arm or DryNites® arm).

The treatment assignment (Discontinuation vs. continuation of DryNites®) will be captured in the EDC from the IWRS.

4.3.6. Patient Withdrawal and Discontinuation of Study Treatment

Any individual participant will be withdrawn from the study if any of the following criteria apply:

- Withdrawal of parents/carers consent, for any reason
- Investigator's decision
- Adverse event (AE)
- Initiation of a prescribed therapy for NE (pharmacologic or bed alarm)

- Severe non-compliance with the study clinical investigation plan, including deviations to eligibility criteria and non-compliance with the study procedures
- Participant's death
- Participant lost to follow-up

Parents/carers may withdraw consent and discontinue the patient's participation in the study at any time, for any reason with no effect on their medical care or access to treatment. If consent is withdrawn prior to completing the study core and/or extension period, the parents/carers will always be asked about the reason(s) and the presence of any AEs. Any known reason for withdrawal should be documented in the electronic case report form (eCRF). The Investigator will follow-up AEs outside of the clinical study.

If a participant is withdrawn from participation in the study, then his/her enrolment code cannot be reused. Withdrawn participants will not be replaced.

All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the participant.

The Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary, due to medical reasons, ineligibility (either arising during the study or retrospectively having been overlooked at screening), significant deviation from the clinical investigation plan, significant non-compliance with study requirements.

The Investigator should document any deviation from the clinical investigation plan regardless of their reasons.

4.3.6.1. Lost to Follow-up

A participant will be considered lost to follow-up if:

- He/she fails to return for scheduled on-site or remote visits
- Randomisation and subsequent visits that cannot be done on-site, cannot be conducted remotely either
- Patient misses a clinic or remote visit and is unable to be contacted by the study centre.

The following actions must be taken if a participant fails to return to the clinic for a required study visit or cannot be contacted over the phone (or video/teleconference) to conduct a scheduled remote visit:

- The study centre must attempt to contact the participant's parents/carers and reschedule the missed visit as soon as possible and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant's parents/carers (at least

2 telephone calls and/or messages). These contact attempts should be documented in the participant's medical record.

- Should the participant's parents/carers continue to be unreachable, the participant will be considered to have withdrawn from the study.

4.3.7. Study Termination by the Sponsor

Kimberly-Clark reserves the right to discontinue the study overall or at any particular site at any time for the following reasons:

- Failure to meet enrolment goals overall or at any particular site
- Emergence of any efficacy/safety information that could significantly affect continuation of the study
- Violation of good clinical practice (GCP), the clinical investigation plan, or the contract by a site or Investigator, disturbing the appropriate conduct of the study

The Investigator/site will be reimbursed for reasonable expenses incurred in case of study termination.

4.3.8. Clinical Investigation Plan Deviations

The following events will be considered as the major violations of the clinical investigation plan and lead to the exclusion of the participant's data from the analysis:

- Absorbent pants/nappies (of any brand) used nocturnally in the 'no pants' group (up to 4 violations of the clinical investigational plan over the 4-week trial period will merit exclusion; these will be documented in the diary)
- No pants, or absorbent pants of a different brand, used nocturnally in the DryNites® group (up to 4 violations of the clinical investigation plan over the 4-week trial period will merit exclusion; these will be documented in the diary)
- Initiation of a prescribed therapy for NE (pharmacologic or bed alarm)

4.4. Study Treatment

4.4.1. Medical Device

DryNites® pyjama pants are absorbent pants manufactured by Kimberly-Clark and designed to reduce the burden of bed-wetting. DryNites® are registered as Class I medical devices and CE marked; they are commercially available since 1995. They are not a treatment for NE and are not designed to cure NE.

DryNites® pyjama pants are available for male and female children in 3 sizes (for children aged 3-5, 4-7 and 8-15 years). It is expected that the 4-7- and 8-15-years sizes will be used in this study.

DryNites® Medical Device Incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the Investigator throughout the study (see Section 4.6.4).

4.4.2. Provision of Study Treatment

DryNites®, defined as the study treatment, is commercially available medical device of Class I and will be provided free of charge to the study participants. DryNites® should be used in accordance to this clinical investigation plan instructions. Study treatment and absorbent bed mats will be supplied to the participants by the Investigator/site; however, the use of bed mats is optional. A 4-week supply will be distributed to each participant's parents/carers at each visit Day 0, Day 28 ± 7 days, and Day 56 ± 7 days. In case of remote visits, study materials will be shipped by the site to the patient's address according to local law and regulatory instructions.

All packages will be labelled "for use in clinical investigation only" (in the applicable local languages).

The younger age group will be provided with the 4–7 years DryNites® size. Parents/carers in the older age group will select whether age 4–7 or age 8–15 DryNites® size is most appropriate.

DryNites® age 4–7 years are provided in packs of 10. As such, each participant will be provided with 4 packs of DryNites® to cover each 4-week period.

DryNites® age 8–15 years are provided in packs of 13. As such, each participant will be provided with 3 packs of DryNites® to cover each 4-week period.

Absorbent bed mats are provided in packs of 12. Each participant randomised in the intervention group (discontinuation of DryNites® pants) will be provided with 3 packs of bed mats to cover each 4-week period. Participants randomised in the control group (continuation of DryNites® pants) will receive 1 pack of bed mats per 4-week period. The use of bed mats is optional.

Any surplus of DryNites® and absorbent bed mats at the end of each 4-week period can be kept by the participant.

4.4.3. Storage/Accountability of DryNites® and Absorbent Bed Mats

All participating centres will be provided with multiple DryNites® sizes for distribution, based on their anticipated enrolment.

Only participants enrolled in the study may receive study treatment and only authorised study centre staff may supply or administer study treatment. All study treatments must be stored in a secure and monitored (manual or automated) area with limited access to the Investigator and authorised study centre staff.

The Investigator, a member of the study centre staffs, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all DryNites® and bed mats supplies using the Device Accountability Form. These forms must be available for inspection at any time.

At the end of the study, all unused materials will be returned by the site to Kimberly-Clark.

4.4.4. Concomitant Therapy

Concomitant therapies not intended to treat NE can be provided as standard of care during the conduct of this study.

4.5. Outcome Definitions and Measures

4.5.1. Primary Outcome Measure

Every morning, starting from the date of parent(s)/carer(s) written informed consent through discontinuation of the study, the parent/carer of the participant will complete an electronic diary to record events from the previous night, including the following details:

- Were absorbent pants worn?
- Was the bed mat used?
- Did the child have an NE event?
- How was the NE event managed? (1 response to be selected: Child slept through the night; child awoke, but did not take any action; child awoke and changed pants/changed bed/visited toilet, but did not disturb parents; child awoke and woke parents)

Please refer to Section 4.7.2 for details.

For both the older and younger participant populations, the primary endpoint will be the average number of wet nights in Week 4/last week of the intervention period.

A clinically significant reduction in NE is considered a reduction of ≥2.0 wet nights per week.

4.5.2. Secondary Outcomes

Quality of Life and sleep quality will be assessed via a set of validated questionnaires for the participants and their parent/carers at each study visit (Day 0, Day 28 ± 7, Day 56 ± 7 and Day 84 ±7 [optional]) or remotely in case of remote visits including baseline. Additionally, the perception of DryNites® attributes, compared to previously used absorbent products will be evaluated through 2 specific questionnaires designed for this study.

Questionnaires will be provided in electronic format and can be administered on-site via hand-held devices or computers or completed remotely via the parent/carer's own device.

As a contingency to restrictions related to the outbreak of Covid-19, the baseline, randomisation, and any subsequent visits could be performed remotely via phone or video/teleconference, if an on-site visit cannot be performed. For remote visits, PRO questionnaires will be accessed through the parent's/carer's own electronic device. The PRO questionnaires will be available after a given visit (and should be completed before the next visit). The PRO questionnaires can also be completed remotely, within the same time window, if completion is not feasible during any on-site visit including baseline.

4.5.2.1. Paediatric Incontinence Questionnaire (PinQ)

The PinQ will be used to assess the child's QoL. The PinQ is a validated cross-cultural continence-specific paediatric QoL questionnaire to assess children with bladder dysfunction, developed by Bower el al (Bower et al. 2006). It is available as self-rated and proxy versions. This will be completed by the child themselves in the older participant group and will be completed by the parent/carer on behalf of the child in the younger participant group.

The PinQ measures the emotional impact that urinary incontinence has on a child. It consists of 20 urinary incontinence QoL related questions divided in 2 dimensions: intrinsic (14 items) and extrinsic (6 items), which are graded on a scale of 0 to 4 (0=No, 1=Hardly ever, 2=Sometimes, 3=Often, 4=All the time) with a total possible global score of 80.

The total score indicates the impact urinary incontinence has on the child's QoL with the higher scores indicating a more significant effect.

4.5.2.2. World Health Organization Quality of Life (WHOQOL) BREF

The WHOQoL-BREF questionnaire (WHO 1996) will be used to assess the parents'/carers' QoL. It will be completed directly by the parent/carer. A general QoL question will be added to the end of the survey, specifically asking their perspectives on how the current management

of their child's NE affects their QoL. The WHOQoL-BREF questionnaire is derived from a larger instrument, the WHOQoL-100. It includes 26 items, grouped in 4 domains: Physical Heath, Psychological, Social Relationships, and Environment, and 2 separate items asking the respondent about overall perception of QoL (item 1) and an individual's overall perception of their health (item 2). It is available in self-rated or interview-based forms.

The scores of items 3, 4 and 5, which are negatively phrased, need to be reversed. The mean score of items within each domain is used to calculate the domain scores, which are converted into a 0-100 scale. Higher scores denote higher QoL.

Where more than 20% of data is missing from an assessment, the assessment should be discarded. Where an item is missing, the mean of other items in the domain is substituted. Where more than 2 items are missing from the domain, the domain score should not be calculated (except for domain 3 [Social relationships], where the domain should only be calculated if <1 item is missing).

4.5.2.3. Paediatric Daytime Sleepiness Scale (PDSS)

The PDSS questionnaire will be used to assess the child's sleep. It is comprised of 8 items assessing daytime sleepiness and rated on a 5-point Likert scale ranging from 4 (Always/ Very often) to 0 (Never); the score of the third item needs to be reversed to calculate the total score. Higher scores indicate greater daytime sleepiness, and were associated with reduced total sleep time, poorer school achievement, poorer anger control, and frequent illness. The scale score is correlated with total hours of night-time sleep (Drake et al. 2003). While no time reference is specifically identified by the questionnaire, items query feelings of drowsiness in a variety of settings over the course of the day. It is validated for administration in children 5-17 years old. This will be completed by the child themselves (with attendance of an adult) in the older participant group and will be completed by the parent/carer on behalf of the child in the younger participant group.

At enrolment, the site will record whether the child takes regular daytime naps; these children will be excluded from the analyses of sleep.

4.5.2.4. Checklist Individual Strength (CIS)

The CIS questionnaire will be used to assess the parents' sleep. This will be completed directly by the parent/carer.

The CIS consists of 20 statements on fatigue-related problems respondents might have experienced in the past 2 weeks. A Likert scoring scheme from 1 to 7 is used. The questionnaire covers measures 4 dimensions of fatigue: Subjective fatigue severity (8 items), Concentration problems (5 items), Reduced motivation (4 items) and Physical activity (3 items). It yields 1

total score and 4 domain scores. On the fatigue severity subscale, a cut-off score of 35 is seen as indicative of severe fatigue. In a study on work absence due to fatigue, a cut-off score of 76 on the CIS indicates a risk for subsequent sick leave or work disability (Bültmann et al. 2000).

4.5.2.5. Absorbent Pants and DryNites® Clinical Trial Questionnaires

The child and parents'/carers' perspectives on their experience with previous absorbent pants/nappies, and on the attributes of DryNites® vs. previously used products will be recorded via 2 specific questionnaires designed for this study and administered at study entry (Absorbent Pants Clinical Trial Questionnaire, about previous products) and at Day 28 ± 7 (DryNites® Clinical Trial Questionnaire).

Each questionnaire includes the following: identification of previous absorbent product (question 1), 2 narrative questions, 11 statements about the absorbent product (responses: Agree, Tend to agree, Neither agree nor disagree, Tend to disagree, Disagree). The Absorbent Pants Clinical Trial Questionnaire includes 6 questions on the attributes of the previous absorbent product, responded on a 1-10 scale (with 1= not at all, and 10 being the highest level of appreciation). The DryNites® Questionnaire includes an overall preference question, responded on a 1-10 scale, and 8 specific questions on preference for DryNites® attributes compared to the previous absorbent product.

4.5.3. Other Assessments

4.5.3.1. Willingness to Continue in the Extension Period

If the child or parents/carers do not wish to participate in the extension trial, their reasons for non-participation will be recorded in the eCRF on Day 56 ± 7.

4.5.3.2. Physical Examination

The baseline visit can be performed remotely.

In case of on-site baseline visit, a complete physical examination will be performed to confirm eligibility for enrolment, with special attention to the external genitalia and the lower back region to exclude any pathology that may cause incontinence in children. It will have 3 components (Haid et al. 2017):

- Body height and body weight, and calculation of the body mass index (BMI). This may detect any issue regarding failure to thrive, growth retardation or the presence of obesity

- External genitalia examination of urethral meatus to exclude epispadias; hypospadias; meatal stenosis; phimosis; labial adhesions
- Examination of the lower back for dimples, hypertrichosis, or a suspect palpatory finding, to possibly point to spina bifida occulta. In addition, an orienting neurological examination (sensitivity, walking pattern) and inspection of the feet (looking for malformations such as clubbing, tight heel cords, and toe mispositioning in patients with neurogenic bladder-emptying disorders) will be performed. Testing the grasp function of the toes is a simple neurological test for an intact S1-S2-S3 innervation.

In case a remote visit is performed, height/weight and full physical examination will not be recorded. In this scenario, the Investigator must check the medical records and/or interview the parent/carer to investigate history of congenital abnormalities of the urinary tract, history of surgery on the urinary tract, and history of verified urinary tract infections before determining eligibility.

4.6. Adverse Events

The definitions, recording and reporting of an AE, SAE or Medical Device Incident can be found in Section 7.

Adverse events will be reported by the participant, parents/carers, or the participant's legally authorised representative.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study treatment.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to product, action(s) taken, and outcome of any sign or symptom observed by the physician or reported by the patient/parents/carers upon indirect questioning.

4.6.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs will be collected from the date of written informed consent granted by the parent(s)/carer(s) onwards until discontinuation of the study at the time points specified in the schedule of assessments.

All SAEs will be recorded in the eCRF within 24 hours of awareness; this will trigger an immediate email notification of the SAE to the Sponsor. The Investigator will record any updated SAE data in the eCRF within 24 hours of it being available; this will trigger an email notification of the SAE follow-up report to the Sponsor accordingly.
Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, they will follow-up any AE ongoing at study discontinuation until resolution or stabilisation.

4.6.2. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up.

4.6.3. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unanticipated serious adverse device effect (USADE) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor, will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

4.6.4. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purpose of NE. In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and

documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

A Medical Device Incident is an event that causes, or has the potential to cause, unexpected or unwanted effects involving the health and safety of patient's, users or other persons.

4.6.4.1. Time Period for Detecting Medical Device Incidents

- Medical Device Incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any incident at any time after a patient has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

4.6.4.2. Follow-up of Medical Device Incidents

- All Medical Device Incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 4.6.2). This applies to all patients, including those who discontinue study treatment.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

4.6.4.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical Device Incidents will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the clinical investigation plan definition of a Medical Device Incident.
- The Medical Device Incident Report Form will be completed in the eCRF using the SAE form. This will trigger an immediate email notification of the Medical Device Incident to the Sponsor.

- The same individual will be the contact for the receipt of Medical Device Incident reports and SAE reports.

4.6.4.4. Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all incidents occurring with any medical device provided for use in the study for the Sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

4.7. Data Sources and Collection

Relevant mandated visits and data time points for the study are presented in the Data Collection Schedule provided below. All data elements will be collected from information reported by the children/parents/carers and will be prospectively recorded by the Investigator for the purposes of the study.

Table 2 Schedule of Assessments

Procedure	**Visit 1 Baseline**[a]	**Visit 2 End of run-in randomisation**	**Visit 3 End of intervention period**	**Visit 4 End of extension period**	**End of study**
	Day 0	Day 28 ± 7	Day 56 ± 7	Day 84 ± 7	
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographics	X				
Medical history	X				
Characteristics of NE	X				
Height and weight[b]	X[b]				
Full physical examination[c]	X				
Prior absorbent pants/nappies used	X				
Adverse events[d]	X	X	X	X	X
Concomitant medication to treat AE	X	X	X	X	X
Daily Diary	→	→	→	→	→

Procedure	Visit 1 Baseline[a]	Visit 2 End of run-in randomisation	Visit 3 End of intervention period	Visit 4 End of extension period	End of study
Review of daily diary[e]		X	X	X	X
Randomisation		X			
Dispensation of DryNites® and bed mats	X	X	X		
Patient/parents/carers QoL and sleep questionnaires[f]		X	X	X	X
Absorbent Pants Clinical Trial Questionnaire	X				
DryNites® Clinical Trial Questionnaire		X[g]			
Reason for discontinuation					X

NE: Nocturnal Enuresis
(a): Baseline visit can be performed remotely.
(b): In case a remote visit is performed, height/weight will not be recorded.
(c): In case a remote visit is performed, a full physical examination will not be recorded. In this scenario, the Investigator must check the medical records and/or interview the parent/carer to investigate history of congenital abnormalities of the urinary tract, history of surgery on the urinary tract, and history of verified urinary tract infections before determining eligibility.
(d): AEs, SAEs and Medical Device Incidents are collected from ICF signature onwards.
(e): Review of diary data by the Investigator/treating physician.
(f): For participants who meet the randomisation criterion.
(g): For all participants at the end of the run-in period.

4.7.1. Visit 1 - Baseline Visit

The baseline visit can be performed remotely.

Informed consent/assent will be obtained prior to participation in the study. Participants will be assigned a unique patient identifier once consent is signed. Eligibility for the study will be assessed at the initial screening visit on Day 0 and confirmed at the randomisation visit on Day 28 ± 7.

The Investigator or delegate will:

- Provide the participant with a study identification card
- Create the patient's and parents/carers profiles on the EDC for record of questionnaires and diary entries
- Show the diary functionality to the participants/parents/carers, explain and remind about the importance of compliance with study assessments
- Provide the parents/carers with all materials (DryNites® and absorbent bed mats) required for the 4-week run-in period after enrolment.

The following assessments will be performed at baseline for all consented patients:

- Eligibility criteria, date of informed consent

- Demographics: age, sex, race
- Height, weight, BMI (calculated)*
- Medical history
- Characteristics of NE: the questionnaire adapted from the established Clinical Management Tool detailed in Table 3 will be completed by the Investigator
- Physical examination**
- Prior brand and type of absorbent pants used
- Administration of the Absorbent Pants Clinical Trial Questionnaire
- Any AE occurred since ICF signature, if relevant
- Concomitant medication for AEs, if relevant.

*In case a remote visit is performed, height/weight will not be recorded.

** In case a remote visit is performed, a full physical examination will not be performed. In this scenario, the Investigator must check the medical records and/or interview the parent/carer to investigate history of congenital abnormalities of the urinary tract, history of surgery on the urinary tract, and history of verified urinary tract infections before determining eligibility.

Table 3 Questionnaire for determination of nocturnal enuresis presence, adapted from the Clinical Management Tool

Determination of monosymptomatic NE	**Exclude**	**Include**
Age (years)	<4 or >8	4–8
Does the child wet the bed at night?	No	Yes
Has the child experienced any dry period for ≥6 months since birth?	Yes	No
Number of wet nights per week	1–6	7
Is the child receiving any treatment for NE?	Yes	No
Has the child received any treatment for NE in the previous 6 months?	Yes	No
Exclusion of underlying bladder dysfunction (Non-monosymptomatic NE)		
Daytime wetting	Yes	No
>8 bladder voids per day	Yes	No
Voiding postponement (>2 times per day)	Yes	No
Sudden and urgent need to urinate (>2 times per day)	Yes	No
Holding manoeuvres observed (>once per day)	Yes	No
Need to strain to pass urine (>once per day)	Yes	No
Interrupted urine stream or several voids one after the other	Yes	No
History of urinary tract infection	Yes	No
Any additional illness related to kidneys and spinal cord	Yes	No
Constipation (<3 bowel movements per week) or faecal soiling	Yes	No
Psychological, behavioural or psychiatric problems (including attention deficit hyperactivity disorder, attention deficit disorder, autism etc.)	Yes	No
History of motor and/or learning disabilities or delayed development	Yes	No

Clinical Management Tool, in Vande Walle et al, 2012

4.7.2. Direct-to-Patient Data Collection

The following data will be collected daily for all enrolled patients using an electronic diary from the morning following the baseline visit until discontinuation from the study:

- Were absorbent pants worn? Yes/No/Another brand
- Was the bed mat used? Yes/No/Another brand
- Did the child have an NE event? Yes/No
- How was the NE event managed? One response to be selected: Child slept through the night; child awoke but did not take any action; child awoke and changed pants/changed bed/visited toilet but did not disturb parents; child awoke and woke parents.

4.7.3. Visit 2 - End of Run-in/ Randomisation Visit

The following assessments will be performed for all patients at end of run-in/randomisation visit (Day 28 ± 7):

- Any AEs occurred since the baseline visit
- Concomitant medications for AEs
- Review of diary data
- DryNites® Clinical Trial Questionnaire (all participants)
- Patient and parents/carers QoL and sleep questionnaires: PinQ, WHOQOL, PDSS, CIS (for randomised participants only)

The Investigator will confirm NE frequency by assessing the data recorded in the diary by the participants/parents/carer at the randomisation visit (Day 28 ± 7). Only participants who experience NE at a frequency of 7 nights per week during the last week of the run-in period (no dry night) will be randomised.

4.7.4. Visit 3 - End of Intervention Period/Enrolment in Extension Period Visit

The following assessments will be performed for all enrolled patients at the end of the core study period:

- Any AEs occurred or ongoing since the previous visit
- Concomitant medications for AEs
- Review of the diary data
- PROs: PinQ, WHOQOL, PDSS, CIS
- Willingness to participate in the extension period
- Complete the Disposition/End of study form for participants not willing to enrol in the extension

4.7.5. Visit 4 - End of Extension Period Visit

The following data will be collected for all enrolled patients at the end of the extension period:

- Any AEs occurred or ongoing since the previous visit
- Concomitant medication for AEs
- Review of the diary data
- PROs: PinQ, WHOQOL, PDSS, CIS

4.7.6. Disposition/End of Study

The following data will be collected for all enrolled patients at the time of discontinuation:

- AEs occurred since the previous visit. All AEs ongoing at the time of discontinuation will be followed up until resolution or stabilisation of for 30 days, whichever occurs first
- Concomitant medication for AEs
- Review of diary data
- PROs: PinQ, WHOQOL, PDSS, CIS (for participants who were randomised)
- Date of completion/discontinuation
- Primary reason for discontinuation

5 STATISTICAL METHODS

5.1. Statistical Hypotheses

The statistical hypothesis behind the present study design is the equivalence in rate of spontaneous resolution of NE at 56 ±7 days between discontinuing and continuing nocturnal use of DryNites® absorbent pyjama pants in children with NE. The margin is set to 2/7 wet nights with an expected proportion of 0.95 and 0.80 wet nights, respectively for continuing and discontinuing use of absorbent pants group. The power is set to 99%.

5.2. Sample Size

The sample size calculation is based on simulations according to the following procedure: During the 4-week trial period, there will be twice as many children assigned to the intervention group (discontinuation of absorbent pants) compared with the control group (continued use of DryNites®). For each child in the 2 groups, the number of wet nights during the last week is simulated from a binomial distribution with n=7 as the number of trials and probabilities p_0=0.95 and p_1=0.80 indicating the risk of a wet night in the control group and intervention group respectively. The simulations are conducted for various sample sizes, each with 1000 simulated data sets. For each data set the risk difference (p_0–p_1) is estimated with a corresponding 95% confidence interval (CI). The 2 methods are said to be equivalent with an equivalence margin δ if CI of the risk difference lies within the interval [-δ, δ]. This is done for different values of δ, here for δ=2/7, 3/7, 4/7 corresponding to 2, 3 and 4 dry nights per week (i.e., 5, 4, and 3 wet nights per week). Finally, the power for each sample size is calculated as the number of estimates with a CI lying within the defined interval [-δ, δ] out of the 1000 simulations.

Fifteen participants are needed in the continuation arm to obtain a power of 99%. This means that a total of 3x15=45 participants are needed at randomisation (due to the 2:1 randomisation). Fifteen additional participants are added to this number (total of 60 participants) to compensate for dropouts/poor compliance during the trial, and for the participants who will be excluded at randomisation because they did not fulfil the criteria of 7 wet nights per week (screen failures). Additionally, the primary endpoint will be analysed separately for the 2 age groups (4–<6 and ≥6–8 years of age) and therefore 60 participants will be needed for each age group (total 120 participants).

The same simulations have been performed with different definitions of equivalence, i.e., 5, 4, and 3 wet nights per week and this showed approximately the same number of participants needed for obtaining 100% power. Similarly, if the assumption of 15% reduction in the control arm is changed to 20% it does not change the conclusions either.

As such, 120 participants should be recruited, with approximately half of the participants should be in the younger age group, age 4–<6 years, and half of the participants should be in the older age group, ≥6–8 years.

5.3. Populations for Analyses

Table 4 Analysis Sets

Analysis Set	Description
Screened Set	All patients consented
Randomised Set	All patients in the Screened Set who are assigned to a randomisation group
Safety Analysis Set	All patients in the Randomised Set
Primary Analysis Set	All patients in the Randomised Set excluding participants with major violations of the clinical investigation plan
Extension Set	All patients in the Randomised Set who participate in the extension period

5.4. Data Analyses

5.4.1. General Considerations

The analysis plan will be fully described in a written and approved statistical analysis plan (SAP). Descriptive analyses will be performed on the Screened Set and the Randomised Set to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. If more than 15% of randomised participants will be excluded from the Primary Analysis Set, the baseline descriptive analysis will be repeated on the primary endpoint analysis population.

Primary and secondary endpoint analyses will be performed before the end of the study, after the last enrolled participant has completed the Day 56 ± 7 days assessments.

Applicable analyses will be repeated as descriptive at the end of the study to include the extension period assessment and will be based on the Extension Set.

All computations and generation of tables, listings and data for figures will be performed using Statistical Analysis System (SAS)® version 9.4 or higher (SAS Institute, Cary, NC, USA).
Continuous variables will be reported as mean (and standard deviation [SD]) along with median and range where appropriate. Categorical variables will be summarised as number and proportion of the total study population, and by age subgroups (4–<6 years and ≥6–8 years) where appropriate.
In general, descriptive statistics of quantitative parameters (result and change from baseline) by scheduled visits will be provided on observed cases, that is, patients having non-missing assessments at a specific visit.
Individual patient data will be presented in listings considering the Screened Set.
All AE verbatim terms will be recorded and coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

5.4.2. Planned Analyses

The total number of patients included in each analysis set along with the number of patients for each of following categories will be provided as disposition analysis:

- Patients consented, overall and by age group (4–<6 years and ≥6–8 years)
- Patients randomised, overall and by age group (4–<6 years and ≥6–8 years)
- Patients who completed the 4-week intervention period, overall and by age group (4–<6 years and ≥6–8 years)
- Patients who entered the extension period, overall and by age group (4–<6 years and ≥6–8 years)
- Patients who completed the extension period, overall and by age group (4–<6 years and ≥6–8 years)
- Time and reasons for discontinuation of the study, overall and by age group (4-<6 years and ≥6–8 years).

For all categories except the Screened Set, the percentages will be calculated using the number of randomised patients as the denominator for each treatment group.

Baseline will be defined as the data collected at or prior to randomisation; demographic and baseline characteristics, disease history, physical examination, medical history and concomitant medication will be summarised with appropriate descriptive statistics by group and separately for age subgroups.

These summaries will be provided for the Screened and Randomised Sets.

Body height, body weight and BMI will be summarised. The calculated BMI will be classified as follows based on comparison with:

- Underweight (<5th percentile for sex and age),
- Normal (from 5th to less than 85th percentile for sex and age),
- Overweight (from 85th to less than the 95th percentile for sex and age),
- Obese (≥95th percentile for sex and age).

Physical examination will be summarised as percentage of patients with normal/abnormal result overall and as per the physical examination features listed in Section 4.5.3.2.

Pathologies associated with past medical or surgical history will be summarised by primary SOC and PT as per MedDRA. Concomitant therapies will be summarised by Anatomical Therapeutic Chemical (ATC) Classification System.

Direct- to-patient data will be analysed descriptively at each assessment along with applicable change from baseline on the Randomised Analysis Set and Primary Analysis Set.

The primary outcome (i.e., average number of wet nights in Week 4 of the core study period) will be analysed for the Primary Analysis Set comparing the 95% CI for the difference between the means of the 2 groups with the predefined margin ($\delta = 2/7$). If the CI lies strictly within [$-\delta$, $+\delta$], the study hypothesis will be demonstrated.

QoL and sleep quality endpoints will be assessed analysing the following questionnaires:

- Paediatric Incontinence Questionnaire
- World Health Organization Quality of Life
- Paediatric Daytime Sleepiness Scale
- Checklist Individual Strength

The PinQ measures the emotional impact that urinary incontinence has on a child. It consists of 20 urinary incontinence QoL related questions which are graded on a scale of 0–4 (0=No, 1=Hardly ever, 2=Sometimes, 3=Often, 4=All the time) with a total possible score of 80.
The total score indicates the impact urinary incontinence has on the child's QoL with the higher score indicating a more significant effect.
The WHOQoL-BREF assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards, and concerns. It comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment. Domain scores are scaled in a positive direction (i.e., higher scores denote higher QoL). The mean score of items within each domain is used to calculate the domain score. Mean scores are then multiplied by 4 in order to make domain scores comparable with the scores used in the WHOQoL-100 (WHO 1996).

The PDSS questionnaire has been developed to measure daytime sleepiness of middle-school children and examine the relationship between daytime sleepiness and school-related outcomes. It consists of 8 items (0–4-point scale) with higher scores associated with reduced total sleep time, poorer school achievement, poorer anger control, and frequent illness. The total score will be calculated as sum of each item response.
The CIS is a 20-item fatigue questionnaire for which the person indicates on a 7-point scale to what extent a particular statement applies to him or her and it measures 4 dimensions of fatigue: fatigue severity (items 1, 4, 6, 9, 12, 14, 16, 20), concentration problems (3, 8, 11, 13, 19), reduced motivation (2, 5, 15, 18) and activity (7, 10, 17). The CIS total score can be calculated by adding the 4 dimensions.
Analyses of these 4 questionnaires will be provided by group on the Randomised Set. Frequency distribution and descriptive statistics, when applicable, will be provided by visit for each item of questionnaires, while summary statistics for total scores, domain scores and changes from baseline will be provided as applicable for the PinQ, WHOQoL-BREF, PDSS and CIS.

The effect size will be also presented as descriptive statistics of ratio between the change from baseline and baseline SD.

The percentage of patients with change from baseline ≥0.5 time the SD will be also provided.

For applicable questionnaires, a covariance analysis model (ANCOVA) with baseline PROs value as covariate will be performed. Group comparisons will be performed for the difference in least squares means (LSMean) at Day 56 ± 7 days. LSMean (standard error [SE]) by group and visit (if applicable), the LSMean difference between groups, along with 95% confidence limits of the group differences and the p-value for the group comparison will be displayed. For the change from baseline, p-value for the within-group difference will also be displayed.

The same analysis will be repeated using a repeated measure model to assess the extension period effects.

The Absorbent Pants Clinical Trial Questionnaire administered at study entry, and the DryNites® Clinical Trial Questionnaire administered at the end of the run-in period, will be analysed descriptively for the Screened Set.

5.4.3. Exploratory Analyses

An exploratory analysis will be presented describing data collected over the extension period.

Additional exploratory analyses may be performed and will be outlined in the SAP prior to analysis.

5.4.4. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

AEs are reported since ICF signature, throughout the patients' discontinuation of the study.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after randomisation and prior to the end of the extension period.

AEs that occurred from ICF signature till randomisation will be described separately.

AEs will be coded using MedDRA. For each group, numbers and proportion of TEAEs, device-related TEAE and serious TEAEs will be tabulated by SOC and PT.

Medical Device Incidents not associated with a TEAE will be described separately.

5.4.5. Handling of Missing Data

Should missing data occur, the data will be analysed as recorded in the study eCRFs, that is, analyses will be performed on patients with non-missing values. However, the number of missing values for data elements will be reported, and the likely impact of missing data on the analysis and the pattern of the missing information will be assessed.

Depending upon the amount of missing data, and whether there is evidence of bias in the missing data (e.g., differences between patients with and without missing data), an imputation strategy, such as multiple imputation, may be performed. If an imputation strategy is undertaken, a sensitivity analysis will be carried out comparing the results from the complete case analysis (where records with missing data will be dropped) and the full set analysis including the imputed data. Full details on handling of missing data will be described in detail in the SAP.

Handling of missing item responses in QoL and sleep questionnaires will be performed according to their respective scoring manuals.

5.4.6. Limitations of Research Methods

The intention of this Phase IV study is to collect data on the impact of absorbent pants on the spontaneous resolution of NE, as well as children and parents/carers QoL and sleep quality. The primary endpoint relies on the completion of a diary by the participant's family. Failure to adhere to the clinical investigation plan and complete the diary information may result in a significant amount of missing data. Information bias will be minimised by using standard eCRF, questionnaires and physicians' training on the study clinical investigation plan. The patients' interpretation and understanding of the questionnaires and different educational backgrounds may also influence the results.

The sites selected will be a convenience sample and may not be representative of the geographic distribution or the clinic/hospital type or size in each of the participating countries. The enrolment will be competitive. At the patient level, consecutive enrolment will be employed to minimise selection bias. Potential selection bias arising from the lack of complete enrolment of potentially eligible patients will be reduced by maintaining screening logs at sites.

Several features of this study have been selected based on the experience of the members of the Scientific Committee. In order to reduce the heterogeneity of the patient population, the study will randomise patients who present with NE every night for 7 months (6 months prior to

baseline, and the 4-week run-in period). These characteristics are shared by most of the patients referred to specialist care. However, selection of patients from hospital/clinic-based specialist care may not be representative of the pool of patients with NE assessed in the community setting by paediatricians and general practitioners.

The equivalence margin of 2 dry nights per week has been determined based on the feedback of patients and families; they would not consider an effect of only 1 night a week clinically significant.

The intervention period is limited to 4 weeks; a longer period may not be acceptable for families. The likeliness of observing a spontaneous resolution of NE in this 4-week period is limited, which carries the risk of concluding to the equivalence of the 2 treatment strategies by lack of any change in either group. The duration of the study period should be kept in mind in the interpretation of the study results.

6 STUDY MANAGEMENT

This study will be performed by IQVIA with guidance, input, review, and approval of Kimberly-Clark, including development of materials, recruitment, training and management of sites, EDC and data management and analysis.

6.1. Data Entry/Electronic Data Capture

All data will be collected and entered directly into the EDC system. The EDC system is designed to meet the 21 CFR part 11 regulations for EDC. All participating sites will have access to the data entered regarding the individual site its own enrolled patients. All sites will be fully trained on using the on-line data capture system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure internet-based EDC registry database via the eCRF. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF should be reviewed, electronically signed, and dated by the Principal Investigator. All changes or corrections to eCRFs are documented in an audit trail and an adequate explanation is required.

For electronic patient-reported outcomes (ePROs), the data entered by the participants/parents/carers will be directly captured into the EDC. The parents will be provided

a link to the EDC at baseline. They will access their ePRO account with a username and password and complete the questionnaires using a site-based electronic device (such as smartphones, iPad or tablet), laptop or desk computer, or parent's own device, if completed off-site.

Similarly, the diary will be directly captured in the EDC, using the patient's own device at home.

6.2. Source Documents

In most cases, the source documents are contained in the patient's medical record and data collected on the CRFs must match the data in the medical records. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the Investigator's site and clearly identifying those data that will be recorded in the CRF, and for which the CRF will stand as the source document. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations.

6.3. File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients, all original signed informed consent forms, copies of all CRFs, SAE forms, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the registry and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 5 years after the release of the final study report. Documents to be archived include the patient enrolment log and the signed ICF. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

6.4. Quality Assurance and Monitoring

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the remote site initiation visit, the monitor will provide training on the conduct of the study to the Investigator, co-Investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. Remote and on-site monitoring will be performed by IQVIA monitors to examine compliance with the clinical investigation plan and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original patient records.

The monitor will close out each site remotely after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a monitoring plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

6.5. **Data Management**

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis.

Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

6.6. Study Governance

A Scientific Committee comprised of 4 members will oversee the conduct of the study. The Scientific Committee is responsible for the following: determination of study objectives and design, review and approval of the study clinical investigation plan, review and approval of the clinical study report, interpretation of the study results and any recommendations based on the clinical study results. The list of members is presented in the Contacts section.

7 SAFETY REPORTING

All AEs, regardless of relationship to the study treatment or intervention, will be monitored and reported throughout the entire course of the study. The AE reporting period begins when the patient is consented to participation in the study (date of first signature of informed consent) and continues through the study discontinuation date. AEs will be recorded on the appropriate eCRF forms.

7.1. Definitions

7.1.1. Adverse events (AEs)

An AE is the development of any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have to have a causal relationship with the product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product, whether or not considered related to the medicinal product. The term AE is used to include both serious and non-serious AEs.

Pre-existing conditions that worsen during a study are to be reported as AEs. If, according to the Investigator, there is a worsening of a medical condition that was present prior to the administration of the intervention, this should also be considered a new AE and reported. Any medical condition present prior to the administration of the intervention that remains unchanged or improved should not be recorded as an AE at subsequent visits.

7.1.2. Serious adverse events (SAEs)

An SAE is any experience that fulfils at least 1 of the following criteria:

- Results in death
- Is life-threatening as it occurred (Patient was at risk of death at the time of the event. This does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Defined as a substantial disruption of a patient's ability to conduct normal life functions
- Results in a congenital anomaly or birth defect
- Constitutes an important medical event (Based upon appropriate medical judgment, event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above)

7.1.3. Medical Device Incidents

A Medical Device Incident is defined as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

The following 3 criteria must be met for an event to constitute an Incident:

- An event has occurred
- The Manufacturer’s device is suspected to be a contributory cause of the incident
- The event led, or might on re-occurrence, lead to one of the following outcomes: death or serious deterioration in state of health of a patient, user or other person

7.1.4. Event severity

Event severity is defined as a qualitative assessment of the degree of intensity as determined by the Investigator or reported to him/her by the patient. The assessment of severity is made irrespective of intervention relationship or seriousness of the event and should be evaluated according of the following scale:

- Mild: The event is noticeable to the patient, but is easily tolerated, and does not interfere with the patient's daily activities.
- Moderate: The event is bothersome, possibly requiring additional therapy, and may interfere with the patient's daily activities.
- Severe: The event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the patient's daily activities.

Note: The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions.

7.1.5. Relationship to treatment

For all events reported, the treating physician or other reporting health care provider will be asked to assess the relationship of the AE/SAEs to DryNites® (if relevant – see below) using the following definitions:

- Probable: A causal relationship is clinically/biologically highly plausible, and there is a correlation between the onset of the AE/SAE and administration of the treatment, and between withdrawal of treatment and resolution of the AE/SAE.
- Possible: A causal relationship is clinically/biologically plausible and there is a correlation between the onset of the AE/SAE and administration of the treatment.
- Unlikely: A causal relationship is improbable, and another documented cause of the AE/SAE is most plausible.
- Unrelated: A causal relationship can be definitively excluded, and another documented cause of the AE/SAE is most plausible.

An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device, as well as any event resulting from use error or from intentional misuse of the investigational medical device.

An unanticipated serious adverse device effect (USADE) unanticipated serious adverse device effect (USADE) is a serious ADE, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report of the medical device.
Relationship to the use of DryNites® should be assessed for any AE occurring during the run-in period and the intervention and extension periods in the control group (participants continuing the use of DryNites® absorbent pants); it is not applicable for the intervention group (participants discontinuing the use of absorbent pants).

7.2. Procedures for Reporting Adverse Events in the Case Report Form

All AEs (serious and non-serious) reported during the study period (from signature of the ICF until study discontinuation) will be captured on the appropriate study CRF.
Each suspected AE occurring during the study must be recorded in the appropriate CRFs and/or specific AE forms as designated by the Sponsor, including the description, seriousness criteria, severity, duration (onset and resolution date), causal relationship with the study device, actions taken with the study device any other required treatment, and outcome.
The following variables will be collected for each AE:

- AE (verbatim)
- Start and stop dates
- Event severity
- Seriousness
- Relationship with the study device
- Action taken with regard to the study device
- Outcome of the AE
- AE caused patient's withdrawal from study (yes or no)

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Criteria for seriousness
- If relevant: date of hospital admission and discharge
- If relevant: date and probable cause of death

- Description of SAE (narrative)

The outcome of each AE (serious or non-serious) should be entered with a term such as those described below:

- Recovered/Resolved
- Recovered with sequelae
- Not recovered/Ongoing
- Change in severity grade (worsening, improving)
- Fatal
- Unknown

If any of the same AEs occur on several occasions in the same patient, then the AE in question must be documented and assessed each time. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

7.3. Procedures for Reporting Adverse Events to Sponsor Consumer Service

In addition to recording the event on the eCRF, all SAEs and non-serious AEs considered related to the use of DryNites® (ADEs) reported during follow-up must also be reported to the Sponsor Consumer Service for purposes of regulatory reporting, using the SAE form. Site personnel must complete and submit the appropriate SAE report form (available through the EDC system) within 24 hours of becoming aware of the event. All SAEs and non-serious AEs considered related to the use of DryNites® (ADEs) occurring after informed consent is signed and until study discontinuation should be reported in the EDC within 24 hours of learning of its occurrence. Once the SAE form is completed is modified in the EDC, this generates an immediate email notification of the SAE to the Sponsor.

In order to maintain compliance with the FDA, EMA and other international and national regulatory bodies, treating physicians may be further contacted by the Sponsor Safety department in order to collect additional information required to evaluate the potential event. AEs/SAEs will be reported to local and regional health authorities by the Sponsor, when appropriate, in accordance with applicable local and regional regulations. The participating

physician is responsible for maintaining compliance with any applicable site-specific requirements related to the reporting of SAEs or other safety information to the local IRB/IEC that approved the study.

7.4. Procedures for Reporting Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a product. Individuals who identify a potential product complaint situation associated with DryNites® pyjama pants should immediately contact by phone the Sponsor Consumer Service and report the event.

Table 5 Sponsor Consumer Service Contact Details

Country	Consumer Service Contact Details
Belgium	0800 194 64
Denmark	clinicaltrial.Drynites@kcc.com
United Kingdom	0800 838 420

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error is associated with an SAE or non-serious AE considered related to DryNites®, an SAE form should be completed and submitted, as described in Section 7.3.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1. Guiding Principles

To ensure the quality and integrity of research, this study will be conducted under the GCP, the International Organization for Standardization (ISO) 14155, the Directive 93/42/EEC, the Declaration of Helsinki and its amendments, and any applicable national guidelines.

The new Regulation (EU) 2017/45 on Medical Devices will fully apply from the 26 May 2020 onwards. Clinical investigations which have started to be conducted in accordance with Article 15 of Directive 93/42/EEC prior to 26 May 2020 may continue to be conducted. As of 26 May 2020, however, the reporting of SAEs and device deficiencies shall be carried out in accordance with this Regulation.

8.2. Required Documents

Prior to the enrolment of any patients in the study, the following documents must be provided by the site to the Sponsor (or their designee):

- Copy of the IRB/IEC approval letter for the clinical investigation plan and informed consent (all written information provided to the patient must be approved by the IRB/IEC)
- Copy of the IRB/IEC-approved informed consent document to be used
- Copy of the clinical investigation plan sign-off page signed by the Investigator
- Fully executed site agreement

8.3. Patient Information and Informed Consent

An ICF (assent form for paediatric patients, if applicable depending on patient's age and local regulations) that includes information about the study in a form understandable to them willbe prepared and given to the patient or the patient's parent(s) or legally authorised representative(s).

This document will contain required elements per the applicable legislation and guidelines. The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the patient, the patient's parent(s), or the patient's legally authorised representative(s) by the Investigator or designee in accordance with the applicable guidelines. The participants will be informed that participation in the study is voluntary and that they can withdraw from the study at any time, without prejudice to their current or subsequent care.

After reading the ICF or assent form, as applicable, the patient or the patient's parent(s) or legally authorised representative(s) must give consent in writing with signature and date. The form should be signed and dated by the patient or by a local legally recognized alternative (e.g., the patient's thumbprint or mark) or by the personally dated signature of the patient's parent(s) or the patient's legally authorised representative. The person conducting the informed consent discussions must also sign and personally date the ICF or assent form.

The ICF and the assent form (if applicable) must be signed by the patient and/or patient's parent(s) or the patient's legally authorised representative(s) before the patient's participation in the study.

The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF and assent form (if applicable) must be provided to the parents/carers or the patient's legally authorised representative. If applicable, it will be provided in a certified translation of the local language. All signed and dated ICFs and assent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF and the assent form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICF and assent form (if applicable), the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICF and assent form (if applicable) for continued participation in the study.

8.4. Patient Confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrolment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the participating countries, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the General Data Protection Regulation (EU) 2016/679.

8.5. Independent Ethics Committee/Institutional Review Board

Consistent with local regulations and prior to enrolment of patients at a given site, the study clinical investigation plan will be submitted together with its associated documents (e.g., ICF, assent form) to the responsible IRB/IEC for its review. Patient enrolment will not start at any site before the Sponsor has obtained written confirmation of a favourable opinion/approval from the relevant central or local IRB/IEC. The IRB/IEC will be asked to provide documentation of

the date of the meeting at which the favourable opinion/approval was given that clearly identifies the study, the clinical investigation plan version, and the ICF version reviewed.

Before implementation of any substantial changes to the clinical investigation plan, the amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the Investigator to have prospective approval of the study clinical investigation plan, amendments to the clinical investigation plan, the ICF and assent form, and other relevant documents, if applicable, from their local IRB/IEC and provide documentation of approval to the CRO. All correspondence with the IRB/IEC should be retained in the Investigator File.

Should the study be terminated early for any unanticipated reason, the Investigator will be responsible for informing the IRB/IEC of the early termination.

8.6. Changes to the Clinical Investigation Plan

Changes to the clinical investigation plan will be documented in written clinical investigation plan amendments. Major (i.e., substantial, significant) amendments will usually require submission to the relevant IRB/IECs for approval or favourable opinion and/or Competent Authorities, if applicable. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained.

Minor (non-substantial) clinical investigation plan amendments, including administrative changes, will be filed by at each participating site and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

8.7. Plans for Disseminating and Communicating Study Results

8.7.1. Study Report

The completed study will be summarised in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings.

8.7.2. Publication Policy

This is an Investigator-initiated trial supported financially by Kimberly-Clark.

The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report and review by Kimberly-Clark.

The full results will be shared in a full publication, anticipated in 2020.

Ogilvy Health will assist with drafting of abstracts and publication manuscripts as required. All clinical trial Investigators involved in drafting abstracts and publication manuscripts will take full responsibility for the methodology and content and will be listed as authors.

9 REFERENCES

Bower WF, Sit FK, Bluyssen N, Wong EM, Yeung CK. PinQ: a valid, reliable and reproducible quality-of-life measure in children with bladder dysfunction. Pediatr Urol. 2006; 2(3):185-9.

Bültmann U, de Vries M, Beurskens AJ, Bleijenberg G, Vercoulen JH, Kant I. Measurement of prolonged fatigue in the working population: determination of a cutoff point for the checklist individual strength. J Occup Health Psychol. 2000; 5(4): 411-6.

Cohen B. Differential Diagnosis of Diaper Dermatitis. Clin Pediatr. 2017; 56(5_suppl):16S-22S.

Coppola G, Constantini A, Gaita M, Sarrauli D. Psychological correlates of enuresis: a case-control study on an Italian sample. Pediatr Nephrol 2011; 26(10): 1829–36.

Drake C, Nickel C, Burduvali E, Roth T, Jefferson C, Badia P. The Pediatric Daytime Sleepiness Scale (PDSS): sleep habits and school outcomes in middle-school children. Sleep 2003; 26(4): 455-8.

Ertan P, Yilmaz O, Caglayan M, Sogut A, Aslan S, Yuksel H. Relationship of sleep quality and quality of life in children with monosymptomatic enuresis. Child Care Health Dev. 2009; 35(4): 469-74.

Feldman M; Canadian Paediatric Society; Community Paediatrics Committee. Management of primary nocturnal enuresis. Paediatr & Child Health 2005; 10: 611–14.

Fleming E. Supporting children with nocturnal enuresis. Nursing Times 2012; 108, 41: 22-25.

Haid B, Tekgül S. Primary and Secondary Enuresis: Pathophysiology, Diagnosis, and Treatment. Eur Urol Focus. 2017; 3(2-3): 198-206.

Kushnir J, Cohen-Zrubavel V, Kushnir B. Night diapers use and sleep in children with enuresis. Sleep Med. 2013; 14(10): 1013-6.

Meydan EA, Civilibal M, Elevli M, Duru NS, Civilibal N. The quality of life of mothers of children with monosymptomatic enuresis nocturna. Int Urol Nephrol. 2012; 44(3): 655-9.

National Institute for Health and Care Excellence (NICE). Clinical Knowledge Summaries. Bedwetting (enuresis) 2014.

National Institute for Health and Care Excellence (NICE). Clinical guideline CG111. Published 2010.

Nevéus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgül S, et al.; International Children's Continence Society. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol. 2010; 183(2): 441-7.

Paediatric Society of New Zealand. Best practice evidence-based guideline: Nocturnal enuresis "bedwetting". 2005.

Tanrıverdi MH, Palancı Y, Yılmaz A, Penbegül N, Bez Y, Dağgülli M. Effects of enuresis nocturna on parents of affected children: case-control study. Pediatr Int. 2014; 56(2): 254-7.

Vande Walle J, Rittig S, Bauer S, Eggert P, Marschall-Kehrel D, and Tekgul S. Practical consensus guidelines for the management of enuresis. Eur J Pediatr. 2012; 171(6): 971–83.

UptoDate. Nocturnal enuresis. Bedwetting in children: Beyond the basics. Available at: https://www.uptodate.com/contents/bedwetting-in-children-beyond-the-basics. Accessed on 07 August 2019.

Urology Care Foundation/American Urological Association. Nocturnal Enuresis (bedwetting). Available at: http://www.urologyhealth.org/urologic-conditions/nocturnal-enuresis- (bedwetting). Accessed on 07 August 2019.

World Health Organization: WHOQOL-BREF: Introduction, Administration, Scoring and Generic Version of the Assessment—Field Trial Version. Geneva: WHO, 1996.

10 APPENDICES

List of stand-alone documents

Informed Consent Form

Paediatric Assent Form

Insurance certificate

Paediatric Incontinence Questionnaire (PinQ)

Paediatric Daytime Sleepiness Scale (PDSS)

WHOQoL-BREF

Checklist Individual Strength (CIS)

Absorbent Pants Clinical Trial Questionnaire

DryNites® Clinical Trial Questionnaire

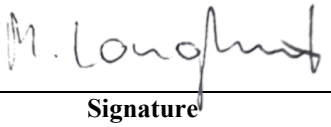
Patient Diary

Patient study identification card

Advertisement for the clinical trial

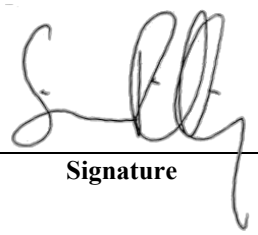
Signature Pages – Sponsor

Clinical investigation plan Reviewed and Approved by:

Marta Longhurst		31 Jan 2022
Kimberly-Clark EMEA Marketing Manager DryNites Walton Oaks, Dorking Road, Tadworth, KT20 7NS, United Kingdom	**Signature**	**Date**
Noam Buchalter		
Kimberly-Clark EMEA Marketing Director Walton Oaks, Dorking Road, Tadworth, KT20 7NS, United Kingdom	**Signature**	**Date**

Signature Pages – Coordinating Investigator

Clinical investigation plan Reviewed and Approved by:

Professor Søren Rittig		05.02.22
Clinical Chair	**Signature**	**Date**
Professor, Consultant		
Paediatrics and Adolescent		
Medicine		
Nephro-Urologic Team		
Aarhus University Hospital		
Palle Juul-Jensens Boulevard 99		
DK-8200 Aarhus N, Denmark		

Signature Pages – Coordinating Investigator

Clinical investigation plan Reviewed and Approved by:

Professor Johan Vande Walle		
Paediatric nephrology	**Signature**	**Date**
Ghent University Hospital		
Heymanslaan 10		
9000 Gent, Belgium		

Investigator Signature Page

Study Title:

Effect of use of DryNites® absorbent pants on the rate of spontaneous resolution of paediatric nocturnal enuresis (NE)

Clinical investigation plan version 3.0 dated 28 January 2022

I have read and understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signature confirms the agreement of both parties that the study will be conducted in accordance with the clinical investigation plan and all applicable laws and regulations including, but not limited to Good Clinical Practices (GCP), International Organization for Standardization (ISO) 14155, and the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

I will provide copies of this clinical investigation plan as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Study. I will discuss the clinical investigation plan with them to assure myself that they are sufficiently informed regarding the conduct of the Study. I am aware that this clinical investigation plan will need to be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached clinical investigation plan and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this clinical investigation plan is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

_____

Print Name

_____ _____

Signature Date

_____

Print Name of Institution or Practice and Location

RETURN ORIGINAL TO IQVIA

RETAIN COPY